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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,645	07/12/2001	Yuri Kolesnikov	830010-2006.	3048

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EXAMINER	
MITCHELL, GREGORY W	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,645	KOLESNIKOV ET AL.	
	Examiner	Art Unit	
	Gregory W. Mitchell	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-9,14,15 and 19-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-9,14,15 and 19-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the Remarks, Amendments and RCE filed April 11, 2005. Claims 1, 9, 15, 23 and 27 have been amended. Claim 30 has been cancelled. Claims 1, 7-9, 14-15, 19-29 are pending and are examined herein.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 11, 2005 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7-9, 14-15, 19-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a **NEW MATTER** rejection. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. The limitations "not to central receptors" in claim 1; "not central or systemic analgesia" in claim 9; "not central receptors" in claim 15; "not to central opiate receptors" in claim 23; and "not to central opiate receptors" in claim 27 do not find support in the application as originally filed. It is noted that said limitations were not in the claims as originally filed. It is further noted that the specification, on page 9, indicated only that a topical formulation of the invention "is not required to deliver active ingredients in the topical formulation to central (brain and spinal cord) opiate receptors." This teaching does not support a limitation wherein the topical formulation *is precluded from* delivering the active ingredients centrally or systemically.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9, 14, 15, 19-23, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yaksh (USPN 5849761) in view of Mayer et al. (USPN 5840731).

Yaksh teaches methods and compositions for the treatment of peripheral hyperalgesia (Abstract). Topical compositions comprising opiates are taught for local administration without eliciting CNS side effects (i.e. those caused by activation of the central receptors) (Abstract). Peripheral use of opiates, such as morphine, is taught as

known in the art (col. 3, line 58-col. 4, line 9). The disadvantage of the use of morphine in the topical compositions disclosed by Yaksh is that it is taught to have short duration of activity and to have systemic and CNS side effects when used at high levels (col. 3, line 58-col. 4, line 9). Effective concentrations of hyperalgesic compounds are formulated in creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, etc. (col. 41, lines 7-12). Alkyl esters of fatty acids, propylene glycol and lecithin are disclosed as excipients for lotions (col. 42, lines 47-50; col. 43, line 50; col. 44, line 1). Aqueous solutions are taught (col. 44, lines 51-63). Yaksh does not specifically disclose a topical composition/method comprising morphine, nor does Yaksh specifically teach an NMDA receptor antagonist. Yaksh does not specifically teach the concentration required to limit the morphine effect to a peripheral effect.

Mayer et al. teaches that the analgesic effectiveness of a combination drug composition comprising at least one analgesic is significantly enhanced by the addition of an NMDA receptor antagonist (Abstract). Mayer et al. teaches compositions comprising a first analgesic, a second component, and an analgesia-enhancing amount of an NMDA receptor antagonist and methods of treatment for alleviating pain by the administration thereof (col. 1, lines 6-27; col. 2, lines 30-col. 3, line 5; col. 4, line 67-col. 5, line 13). Analgesics are taught to be selected from fentanyl, morphine, etc. (col. 3, lines 57-65). NMDA receptor antagonists are taught to be selected from ketamine, etc. (col. 4, lines 33-50). Excipients such as condensation products of ethylene oxide are also taught (col. 5, line 14-col. 6, line 11). Administration is taught to be achieved orally,

rectally, intravenously, intramuscularly, subcutaneously, intrathecally, epidurally, or intracerebroventricularly (col. 4, line 66-col. 5, line 3). It is also noted that the composition of Example 1 comprises about 4% of an opioid analgesic (codeine phosphate).

It would have been obvious to one of ordinary skill in the art to formulate a topical composition, as instantly claimed, comprising morphine and ketamine for only peripheral use because (1) Yaksh teaches that the formulation of morphine for only peripheral use is known in the art when the concentrations are sufficiently low; and (2) Mayer et al. teaches that the addition of an NMDA receptor antagonist (e.g. ketamine) to an analgesic composition is known in the art to significantly enhance the analgesia provided thereby. One would have been motivated to prepare and utilize such a composition because of an expectation of success in providing a topical composition suitable for peripheral relief with significantly enhanced analgesic effects, as taught by Mayer et al., at a concentration low enough to avoid the systemic and CNS side effects of morphine taught by Yaksh.

Furthermore it would have been obvious to one of ordinary skill in the art at the time of the invention to arrive at a composition comprising the claimed amount of morphine because Yaksh teaches that it is known in the art that the concentration of morphine must be sufficiently low to avoid systemic and CNS side effects. It would have been obvious to the skilled artisan to optimize the concentration of morphine in the composition in order to avoid systemic or central delivery because "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the

optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Claims 7, 8, 24, 25, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yaksh and Mayer et al. as applied to claims 1, 9, 14, 15, 19-23, 26 and 27 above, and further in view of Mackles et al. (USPN 5322683).

Yaksh and Mayer et al. apply as disclosed above. The references lack the teaching of a local anesthetic.

Mackles et al. teaches that lidocaine is a topical analgesic (col. 3, lines 16-18).

It would have been obvious to one of ordinary skill in the art at the time of the invention to add the lidocaine of Mackles et al. to the composition of the combined reference because (1) the combined references teach a topical analgesic composition; (2) Mayer et al. teaches the use of a second analgesic; and (3) Mackles et al. teaches that lidocaine is a topical analgesic. One of ordinary skill in the art would have been motivated by an expectation of success in providing a second analgesic in further alleviating pain, as taught by Mayer et al.

Response to Arguments

Applicant's arguments with respect to the pending claims have been considered but are moot in view of the new ground(s) of rejection. Examiner addresses Applicant's argument as they apply to the instant rejections below.

Applicant's arguments that the prior art does not teach a composition and treatment useful exclusively for use in the periphery are not persuasive in view of the new grounds of rejection because Yaksh teaches that topical compositions of morphine are known to affect only the periphery when administered in suitable concentrations.

Likewise, Applicant's arguments that morphine is ineffective in the periphery are not persuasive given the combined teachings of Yaksh and Mayer et al. Yaksh teaches that topical compositions of morphine are known to affect only the periphery when administered in suitable concentrations and Mayer et al. teaches that the combination of morphine with an NMDA receptor antagonist such as ketamine significantly enhances the analgesic effect of the analgesic. Accordingly, not only does Yaksh teach that morphine is known for peripheral use, but Mayer et al. teaches that even at the low concentrations required for limiting morphine to peripheral use, the analgesic effect of such a topical composition would be significantly improved by the addition of an NMDA receptor antagonist, such as ketamine.

Applicant's arguments that Mayer et al. is non-analogous art is not persuasive because Examiner has relied on Yaksh to teach the peripheral effect of opiates and has relied on Mayer et al., primarily, to show that the combination of NMDA receptor antagonists with analgesics, such as morphine, are known in the art to be significantly advantageous.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory W Mitchell whose telephone number is 571-272-2907. The examiner can normally be reached on M-F, 8:30 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

gwm

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER